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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/756,818	01/13/2004	Stephen James Russell	07039-416002	2374

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EXAMINER	
LIETO, LOUIS D	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 12/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/756,818	RUSSELL ET AL.	
	Examiner	Art Unit	
	Louis D Lieto	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 7/1/04.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 19-26 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 19-26 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09197056.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment to the specification was received on 7/01/2004. Claims 1-18 were canceled on 1/13/2004. Claims 19-26 are pending in the instant application

Priority

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C., to U.S. Application Serial No. 09/197,056, filed November 20, 1998, to International Application Serial No. PCT/GB98/02693, filed September 7, 1998, to U.S. Provisional Application Serial No. 60/083,657, filed April 30, 1998, U.S. Provisional Application Serial No. 60/076,448, filed March 2, 1998, to U.S. Serial No. 09/197,056, filed November 20, 1998; PCT/GB98/02693, filed September 7, 1998, to U.S. Provisional Application Serial No. 60/083,657, filed April 30, 1998 and to U.S. Provisional Application Serial No. 60/076,448, filed March 2, 1998.

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d) or (f), to United Kingdom Application Serial No. 9718872.6, filed September 6, 1997

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 19-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method comprising a) transfecting a cell with a nucleic acid sequence encoding a protein operably linked to a tetracycline regulatable promoter *in vitro*, and b) increasing expression of the protein using tetracycline *in vitro*, does not reasonably provide enablement for administering the cells to a mammal that has had an immune response against the protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The claims require increasing expression of a protein in a cell after it has been administered into a mammal, wherein said mammal has had an immune response against said protein prior to administering the cells. The only disclosed purpose for such methods is for therapy (e.g. pg 2, line 12, "cancer therapy"; pg 3, lines 2 1-23, "leukocytes that elicit an anti-tumor effect" pg 8, line 24, "therapeutic (immunogenic) protein").

However, the combination of vector, promoter, level of expression, target tissue, dosage and route of administration required to obtain a therapeutic effect using gene therapy were unpredictable at the time of filing. In Ross et al. (Sept. 10, 1996, Human Gene Therapy, Vol. 7, page 1781-1790) the *ex vivo* approach used to treat tumors resulted in only one melanoma patient **who might be** considered to have had a clinical response, however it may have occurred spontaneously because melanoma is known to regress spontaneously (page 1786, column 1, paragraph 2). Ross et al concludes that it is unpredictable whether a therapeutic result can be obtained using *ex vivo* gene therapy (page 1786, column 1, paragraph 2). Verma et al. (Sept. 18, 1997, Nature, Vol. 389, pages 239-242) states the *in vivo* approach of gene therapy is

unpredictable because of an inability to deliver genes efficiently and to obtain sustained expression (see page 239, 3rd column, line 10). "Although more than 200 clinical [gene therapy] trials are currently underway worldwide, with hundreds of patients enrolled, there is still no single outcome that we can point to as a success story" (page 239, column 1, line 16). Thus, the state of the art of gene therapy is such that there is a lack of correlation between expression of a gene product and therapeutic effect using gene therapy methods.

To further support the unpredictability of the combination of elements required to obtain a therapeutic effect using gene therapy, the following references are provided: Miller et al. (1995, FASEB J., Vol. 9, pages 190-199) reviews the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances in targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain M. (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art, which show promise, but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Crystal R.G. (1995, Science, Vol. 270, page 404-410) also reviews various vectors known in the art and indicates that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409).

The specification demonstrates transfecting Jurkat cells with a vector encoding a chimeric T-cell receptor (TCR) operably linked to the tetracycline operator and encoding tTA. The expression of the TCR is increased by decreasing the concentration of tetracycline *in vitro* (page 31). The specification does not teach administering cells to any mammal, regulating protein expression in a mammal, obtaining a therapeutic effect, how to use cells expressing TCR *in vivo*, how to increase expression of the TCR after the cells have been administered to a mammal, why such cells would be administered to a mammal having an immune response against the TCR. The specification does not correlate the cells expressing TCR to cells expressing a protein that could be therapeutic in a mammal that has had an immune response to the protein. Overall, the specification does not overcome the unpredictability in the art by teaching the level of expression, route of administration, vector, promoter or cells required to obtain a therapeutic effect. Given the lack of guidance provided in the specification taken with the unpredictability in the art, it would have required one of skill in the art undue experimentation to determine the parameters required to obtain a therapeutic effect using the method claimed.

Further, merely increasing expression of a protein in the absence of therapeutic effect does not have a disclosed use in a mammal having an immune response to the protein prior to administering the cell. The only disclosed purpose for such methods is for therapy (e.g. pg 2, line 12, "cancer therapy"; pg 3, lines 2 1-23, "leukocytes that elicit an anti- tumor effect" pg 8, line 24, "therapeutic (immunogenic) protein"). The specification does not overcome the art established unpredictability of gene therapy by teaching the level of expression, route of administration, vector, promoter or cells required to obtain a therapeutic effect. Pg 16, line 26,

through pg 18, line 14 teaches how to make cells encoding a protein operably linked to a promoter. Additionally, Pg 17, lines 14-29, for example teaches how to make a lymphocyte transfected with a vector encoding a T-cell receptor operably linked to a regulatable promoter. However, it cannot be determined how to use such a cell for therapy upon being introduced into a host. Pg 10, line 9, thorough pg 16, line 24, teaches regulatable promoter systems but does not teach the combination of elements required to treat a patient. Further, the specification does not enable administering the cell to a mammal and increasing expression of the protein *in vivo*. While the specification does discuss suitable drug-regulatable promoters, the only one described is the Tet promoter. However, the specification does not provide adequate guidance on the use of the Tet promoter or any other promoter to regulate protein expression *in vivo* or to determine the combination of elements required to use the method claimed to obtain a therapeutic effect. For example, pg 15, lines 14-2 1, teaches a vector encoding GM-CSF under the control of a Tet promoter; however, it cannot be determined how to use such a vector for therapy or why one would obtain a mammal having "an immune response against a polypeptide" such as GM-CSF and administer a vector encoding GM-CSF to such an mammal. Third, the specification does not teach how to regulate protein expression *in vivo*. The specification does not provide adequate guidance to regulate protein expression *in vivo* or to determine the combination of elements required to use the method claimed to obtain a therapeutic effect.

Miller et al. (May 1, 1997, Human Gene Therapy, Vol. 8, pages 803-815) teaches the gene regulation system that cap be applied to gene therapy in humans is yet unknown (page 809, column 2, line 42). Applicants do not demonstrate regulating any genes in humans or in any art recognized *in vivo* model. Without such guidance, the specification does not enable regulating

the expression of a transgene in a mammal as claimed. In particular, the specification does not enable regulating the expression of a polypeptide by "altering the amount of regulatory drug" after the cell has been administered as encompassed by claim 19. The specification does not teach dosage, routes of administration or methods of targeting cells transfected with the polypeptide such that expression can be regulated after the cells have been introduced.

The claims are directed toward various regulatable systems including the tetracycline system. Miller et al. teaches that it is unpredictable which cells the tetracycline system may be applied to (page 809, column 2, 2nd 111 paragraph). Applicants demonstrate transfecting T-cells with a chimeric TCR under the control of a tetracycline system and controlling expression *in vitro* (page 29), but do not correlate the results obtained to other cell lines such that any cell line is enabled. Thus, if applicants intend to claim using the tetracycline regulatory system, the claims should be limited to T cells, which are enabled in the specification. Without adequate guidance as to which cells can be used to express proteins using the tetracycline regulatory system, it would require the skilled practitioner undue experimentation to determine which cells can be used with the tetracycline regulatory system.

Given the lack of guidance in the specification on how to regulate any cells expression of a nucleic acid sequence encoding a immunogenic polypeptide *in vivo*, the lack of guidance on producing any therapeutic affect by administering the cells to any mammal with an immune response to the polypeptide, the art taught unpredictability of obtaining a therapeutic effect using gene therapy, the lack of teachings of any other drug-regulatable promoter for use i*n vitro*, a practitioner skilled in the art would be unable to practice the invention as claimed, except as a method comprising a) transfecting a T cell with a nucleic acid sequence encoding a protein

operably linked to a tetracycline regulatable promoter *in vitro*, and b) increasing expression of the protein using tetracycline *in vitro*, without arduous and extensive experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims19-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 19 is indefinite because the metes and bounds of what the applicants mean by "altering the amount of regulatory drug" in step (c) cannot be determined. The term "altering" encompasses a range of changes from reducing the amount of drug administered to zero or raising it to near toxic levels. Further the specification does not define what the term "altering" means. Claims 20-26 depend on claim 19.

Claims 19-26 appear to be free of the prior art of record because the prior art of record did not teach a method comprising: i) obtaining a mammal that exhibits an immune response against a protein; ii) obtaining cells comprising a vector comprising a regulatable promoter operably linked to a nucleic acid sequence encoding said protein; iii) introducing cells to a mammal; and iv) increasing/decreasing the concentration of an inducing agent to the cells are exposed thereby causing an increase in expression of said protein.

All claims free of the prior art of record

No claims allowed

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Lou Lieto whose telephone number is (571) 272-2932. The examiner can normally be reached on Monday-Friday, 9am-5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Amy J Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is (703)-872-9306. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Patent applicants with problems or questions regarding electronic images that can be viewed in the PAIR can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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